EXHIBIT Q

Hyaluronic Acid Fillers: A Comprehensive Review

Karen L. Beasley, M.D.,[1] Margaret A. Weiss, M.D.,[2] and Robert A. Weiss, M.D.[2]

ABSTRACT

Over the past decade, the popularity of nonsurgical cosmetic procedures has increased exponentially. Last year, according to the American Society of Aesthetic Plastic Surgery, more than 5 million procedures were performed using cosmetic injectables such as botulinum toxin and dermal filling agents.[1] According to the society's recent statistics, more than 85% of all dermal filler procedures occurred with a hyaluronic acid derivative. These numbers are expected to rise in the future as there is currently no other class of filling agent that rivals the popularity of hyaluronic acid. The popularity of hyaluronic acid specifically stems from its effectiveness, ease of administration, and safety profile.

KEYWORDS: Soft tissue augmentation, skin rejuvenation, hyaluronic acid, Restylane, Perlane, Juvéderm, Elevess, Prevelle Silk, Puragen

Use of filling agents to replace the volume loss of intrinsic aging and create a more youthful appearance is one of the most popular cosmetic procedures available. The rate of new filling agents that are launched into the cosmetic market parallels the increase in the popularity of these cosmetic procedures. Hyaluronic acid fillers are particularly popular because they have a low potential for allergic reaction and require no skin testing. Although they are not permanent, most of these agents have a significant length of duration. The procedure is relatively quick to perform, and the patient feels little discomfort if the appropriate pain management techniques are used. This article will review the composition, specific differences, and pivotal clinical studies of all the hyaluronic acid fillers currently available in the United States. A brief description of our clinical experience with hyaluronic fillers is also included. As of December 31, 2008, there are nine U.S. Food and Drug Administration (FDA)-approved hyaluronic acid fillers: Restylane, Perlane, Juvéderm Ultra, Juvéderm Ultra Plus, Elevess, Prevelle Silk, Hylaform, Hylaform Plus, and Captique. A new hyaluronic acid product, known as Puragen Plus in Europe, is projected to be FDA approved in spring 2009 and may be approved by the time of this article's publication.

HYALURONIC ACID

In 1934, a biochemist at Columbia University, Karl Meyer, and his research assistant, John Palmer, isolated a previously unknown substance from the vitreous of cows' eyes that they named hyaluronic acid.[2] Subsequently, hyaluronic acid (HA) was identified in human tissue, as well as in all species of animal. HA shares the same chemical structure across all species and in all tissue types. It is a naturally occurring glycosaminoglycan that composes the extracellular matrix of connective tissue, synovial fluid, and other vital tissues, like the vitreous of the eye, cartilage, fascia, and umbilical cord. Nearly 25 years of biochemical research was required to

[1]Department of Dermatology, University of Maryland School of Medicine, Baltimore, Maryland; [2]Department of Dermatology, The Johns Hopkins University School of Medicine, Baltimore, Maryland.

Address for correspondence and reprint requests: Karen L. Beasley, M.D. The Maryland Laser, Skin, and Vein Institute, 54 Scott Adam Road, Suite 301, Hunt Valley, MD 21230 (e-mail: kbeasley@mdlsv.com).

Injectable Fillers; Guest Editor, Theda C. Kontis, M.D., F.A.C.S.

Facial Plast Surg 2009;25:86–94.

DOI 10.1055/s-0029-1220647. ISSN 0736-6825.

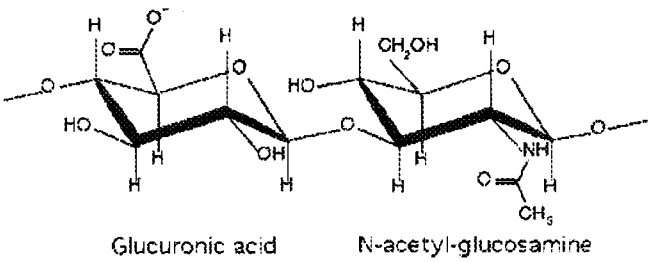

Figure 1 The chemical composition of a hyaluronic acid subunit.

establish the specific chemical composition of HA.[3] Specifically, HA consists of repeating polyanionic disaccharide units of glucuronic acids and *N*-acetyl-glucosamine connected by alternating β 1–3 and β 1–4 bonds (Fig. 1). In the skin, it provides structure and volume while also maintaining and attracting moisture. As the skin ages, the amount of HA decreases and directly correlates with moisture loss and the formation of rhytides. Clinically, the injection of HA into the skin replenishes volume and revitalizes the skin's appearance.

The currently available HA fillers are manufactured similarly but with some distinct differences. The main differences that we will examine are the sources of HA, cross-linking procedure, gel consistency properties (or rheology), and HA concentration. HA fillers may be derived from either an animal or a non-animal source. The animal source of HA is derived from isolating and purifying HA in rooster combs. Rare patients may develop allergic reactions if they are sensitive to the residual avian proteins that may exist in these products. The fillers that are non-animal stabilized hyaluronic acids (NASHAs) are manufactured by the fermentation of *Streptococcus equi* bacterium. These also may contain trace amounts of bacterial proteins and should not be used in patients with known hypersensitivity to streptococcal or gram-positive bacteria. The only animal-based HAs currently available are from the Hylaform family, which is being phased out. Soon, the only available HA products will be bacterial based, otherwise known as NASHAs.

Each company manufactures their HA product differently, but they all begin by mixing a powderized form of HA with water to create a solution. HA is extremely water soluble and potently binds to water in tissue to create its volumizing effect. For example, 1 g of HA can bind 6 L of water.[4] If the aqueous form of HA was injected into the skin, it would be rapidly metabolized into carbon dioxide and water over the course of just a few days. Therefore, the HA must be stabilized into a form that can produce a long-lasting cosmetic effect. The stabilization process occurs by cross-linking the HAs so they can survive rapid degradation in the skin. Currently, four different cross-linking chemicals are used. The Restylane/Perlane and Juvéderm families of products use butanediol diglycidyl ether (BDDE). Prevelle Silk, Captique, and the Hylaform family use divinyl sulfone (DVS). Elevess uses biscarbodiimide (BCDI), and Puragen uses 1,2,7,8-diepoxyoctane (DEO). According to the Material Safety Data Sheets of all of these chemical cross-linkers, they can be irritating and even toxic to the skin. Thus, after these chemicals have caused bonding in the HA, any residual active stabilizer must be removed. Most products are cross-linked with single ether bonds. Only the Puragen family of products undergoes a two-stage double cross-linking process with ether and ester bonds with a proprietary DXL technology. The addition of ester bond linkages, which are hydrophobic, is thought to confer increased stability and protection from hyaluronidase and free-radical degradation.[5]

The cross-linking process may then be modified to create either a particulate or nonparticulate form of HA. In the particulate forms, a firm HA gel is formed and then is pushed through various-sized screens to create different-sized particles. In contrast, nonparticulate HA is created in two stages; first by cross-linking long chains of HA with ether bonds and then a second round of ether bonding to link shorter HA chains to this network. This creates a network of short and long HA chains in a homogeneous gel mass. Currently, the only FDA-approved HA products that have a nonparticulate gel form is the Juvéderm family of products. Their homogenous nonparticulate gels are created with a proprietary Hylacross technology. This technology creates a smooth consistency gel formulation. (See Fig. 2 for a visual comparison of particulate and nonparticulate HA gels.) Particulate HA products depend on particle size to produce greater filling power and longevity, whereas nonparticulate HA gels depend on greater cross-linking to produce greater filling power and longevity. The optimal degree of cross-linking is currently undefined. A very high degree of cross-linking could reduce water's ability to bind to HA and therefore create tissue lift or it could potentially affect the biocompatibility of the filler and cause rejection or encapsulation.[6]

Rheology is the science of deformation and flow of matter. Fluid rheology describes the consistency and flow properties of a liquid or gel. The measure of gel hardness, particle size within the gel, and concentration of HA are key properties that influence a product's rheology. Gel hardness, or G', is a measure of how much gel will be displaced based on the degree of stress

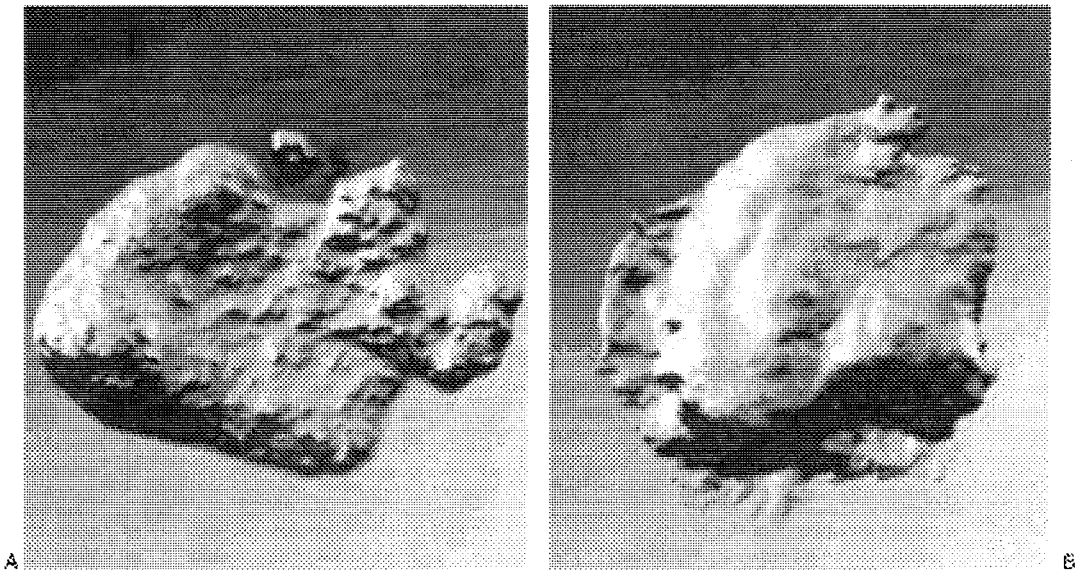

Figure 2 (A) Magnification (2.4x) of a particulate HA gel (Restylane). (B) Magnification (2.4x) of a nonparticulate gel (Juvéderm Ultra).

applied to the gel. For example, products with a high G' are firm gels that require more pressure on the syringe to inject. Because they resist deformation, gels with a higher G' may feel firmer under the skin. Firm gels may cause more tissue disruption when injected, which could lead to more discomfort and swelling than that of products with a lower G'. Products with a low G' are soft gels and require less pressure on the syringe to inject. Because the products with low G' do not resist deformation as well, they feel softer under the skin. Soft gels may be better suited in an area of thinner and softer skin like the periorbital area and lips (Fig. 3). HA particle size also influences product rheology. Products with larger particles or thicker consistency require a larger-bore needle (27-gauge needle) for injection. These more robust products are better used to fill deep folds and to create volume. Products with smaller particles or less viscous products can use a smaller-bore needle (30-gauge needle) for injection. These products are better used for moderate folds and in areas of thinner skin like lips and

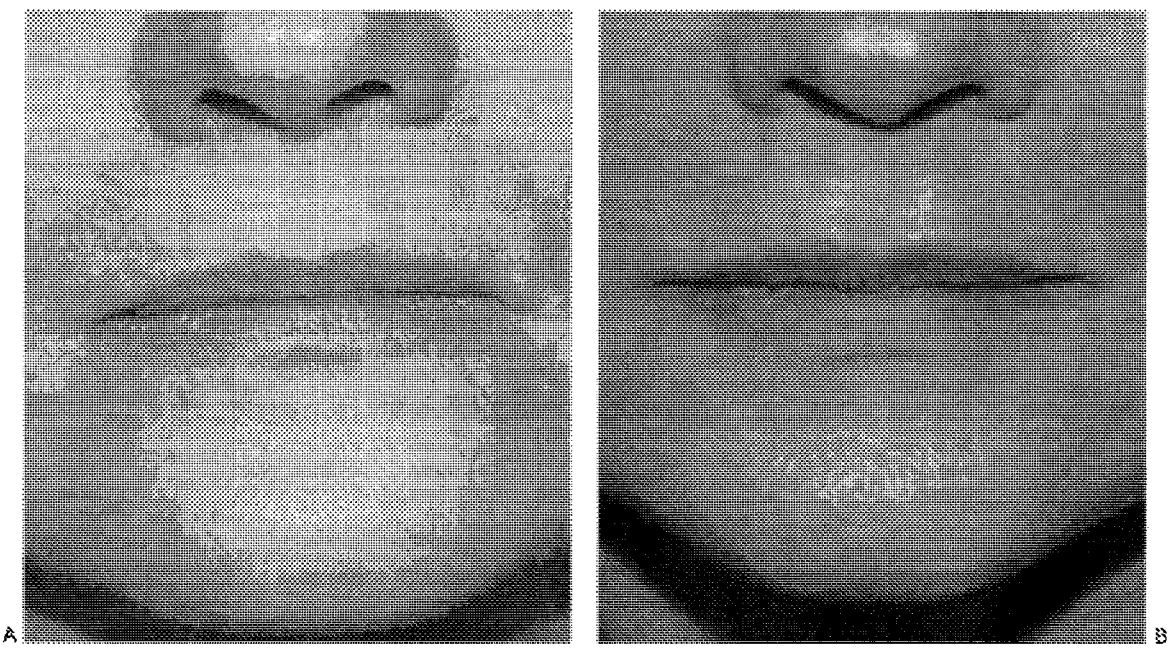

Figure 3 (A) Loss of lip structure and early lateral lip downturn before treatment. (B) Four weeks after treatment of the vermillion border with 0.8 mL of a low G' HA gel (Juvéderm Ultra).

Table 1 Physical Properties of HA Dermal Fillers

	Hylaform	Hylaform Plus	Prevelle Silk	Restylane	Perlane	Juvederm Ultra*	Juvederm Ultra Plus*	Elevess†
Total HA concentration (mg/mL)	5.5	5.5	5.5	20	20	24	24	28
% Cross-linked HA	12	12	12	<1	<1	6	8	N/A
Gel/fluid ratio	98/2	98/2	98/2	75/25	75/25	90/10	90/10	100/0
HA gel concentration (mg/mL)	5.4	5.4	5.4	15	15	17.3	17.3	28
G' modulus (Pa)	140–220	140–220	230–260	660	588	170	200	329
Average particulate size (μm)	500	700	350	300	650	—	—	200
Anesthetic included	No	No	Yes	No	No	No	No	Yes

*Data provided by Allergan.
†Data provided by Anika Therapeutics
N/A, data not available.

around the eye. Total HA concentration refers to the measure of insoluble HA and soluble HA in a product. The soluble or liquid form of HA is absorbed very quickly and is added to some products to improve lubrication and flow through the needle. The insoluble gel portion that persists in the skin after injection is the amount of HA that contributes to the clinical effect. The total HA concentration is well known in all the products, but the calculation of the active amount of gel is often debated among the manufacturers. Table 1 summarizes the physical properties of the available HA preparations.[7–9] Physical properties of a polymer like HA can be difficult to compare because they are not calculated at the same time under the same set of conditions.

We have a vast amount of experience with cosmetic injectibles. The products we have the most experience with are the Restylane/Perlane and Juvéderm families. All of the currently available HA fillers are indicated by the FDA for injection into the mid to deep dermis for the correction of moderate to severe facial wrinkles and folds, specifically nasolabial folds (NLFs). However, HA products are routinely used for off-label indications. Only FDA-approved dermal fillers should be used for injection. If you are using non–FDA-approved fillers and you have a complication, your malpractice insurance will not cover you. It is also imperative to purchase your products from the U.S. distributor. Buying from alternative sources may be less expensive; however, you may be buying a counterfeit substance. These products could be contaminated, expired, or extremely unsuitable for cosmetic injection.

RESTYLANE

Restylane is manufactured by Q-Med (Uppsala, Sweden) and distributed by Medicis Aesthetics (Scottsdale, AZ). It is a particulate form of NASHA that is cross-linked with BDDE. Available in Europe since 1996, this product has been used in more than 10 million treatments worldwide. It was FDA approved in December 2003, after proving superiority to bovine collagen (Zyplast [Allergan, Santa Barbara, CA]) in a randomized, double-blinded, split-face study by Narins et al.[10] Restylane is the first and only NASHA to demonstrate the induction of type 1 collagen in the dermis.[11] In the study, 11 individuals, with a mean age of 74 years, had Restylane injected in one dorsal forearm and a saline control injected in the other. Skin biopsies were taken at 4 and 13 weeks. De novo synthesis of collagen was assessed using immunohistochemical analysis, quantitative polymerase chain reaction, and electron microscopy. It was hypothesized that the increased collagen may be due to stretching and activation of fibroblasts. Persistency data from initial trials suggested a 6-month duration; however, recent research showed after initial treatment with Restylane filler and one retreatment, results persisted for up to 18 months.[12] Specifically, 97% of patients had improvement of at least one grade up to 18 months and 57% of patients had improvement by at least 2 grades up to 18 months. The response was equivalent whether the patients were retreated at 4.5 versus 9 months.

PERLANE

Perlane is also manufactured by Q-Med (Uppsala, Sweden) and distributed by Medicis Aesthetics (Scottsdale, AZ). Particle size is the only difference between the Perlane and Restylane gel formulations (Fig. 4). The largest fraction of gel particles for Perlane is between 940 and 1090 μm, whereas the largest fraction for Restylane is between 250 and 500 mμ. Because the particles in Perlane are larger, a 27-gauge needle is required for injection. There are ~10,000 particles per milliliter in Perlane as opposed to 100,000 particles per milliliter in Restylane. Perlane was FDA approved in May 2007 and is indicated for deep dermal to superficial subcutaneous injections. In its pivotal U.S. trial, Perlane was compared with bovine collagen (Zyplast) in a randomized, blinded, split-face comparison in the correction of NLF.[13] At 6 and 9 months, Perlane was judged to be superior to Zyplast in 50% and 48.8% of patients, respectively. In addition, optimal cosmetic correction was achieved with a smaller volume

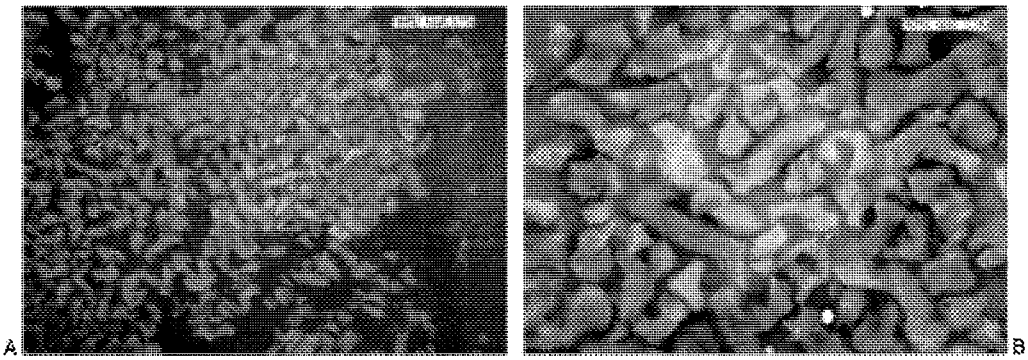

Figure 4 (A) Microscopic appearance of Restylane particles. (B) Microscopic appearance of Perlane particles.

of Perlane. Zyplast required a mean of 2.1 mL per fold, as opposed to Perlane, which required only 1.2 mL per fold. Perlane was also compared against Restylane in correction of NLF in 150 patients, composed primarily of African-American females.[14] At 6 months, 71% of the Perlane-treated and 73% of the Restylane-treated NLFs maintained at least 1 point improvement above baseline. The main difference in this study between the two products was that Perlane was injected in a deeper plane than was Restylane and Perlane also required slightly less volume than did Restylane to produce correction.

JUVÉDERM ULTRA AND JUVÉDERM ULTRA PLUS

Juvéderm Ultra and Juvéderm Ultra Plus are manufactured by Corneal (Paris, France) and distributed by Allergan (Santa Barbara, CA). They are the only nonparticulate forms of NASHAs currently available in the United States. Juvéderm Ultra Plus has a slightly different gel formulation than that of Juvéderm Ultra. During the cross-linking process, more BDDE is added and a greater degree of cross-linking occurs resulting in a gel that has about a 20% thicker viscosity. They were FDA approved in 2006, based on results from their U.S. pivotal trial, which compared both Juvéderm Ultra and Juvéderm Ultra Plus against Zyplast for NLF correction.[15] Both were found to be superior to Zyplast in initial and sustained correction. An additional extended follow-up trial studied the same subjects.[16] It showed that 75% of Juvéderm Ultra–treated patients and 81% of Juvéderm Ultra Plus–treated patients maintained at least 1 grade improvement after 9 months and 68% of Juvéderm Ultra–treated patients and 78% of Juvéderm Ultra Plus–treated patients maintained at least 1 grade improvement after 12 months.

ELEVESS

Elevess is manufactured and distributed by Anika Therapeutics (Woburn, MA). It was FDA approved in December 2006. It is a particulate form of NASHA cross-linked with BCDI. It also contains 0.1% sodium metabisulfite, which is an added antioxidant but cannot be used in patients with a sulfite allergy. Sulfite allergy in the general population is unknown and probably low but is seen more frequently in asthmatic patients. Sulfite allergy can manifest as light-headedness, asthmatic episodes, gastrointestinal or dermatologic symptoms, and anaphylaxis. Elevess has the highest concentration of total HA available at 28 mg/mL. It also was the first HA to be FDA approved to contain 0.3% lidocaine. Its pivotal trial demonstrated noninferiority of Elevess to human collagen (CosmoPlast [Allergan, Santa Barbara, CA]) in augmentation of the NLF.[17] Elevess also required less product (a mean volume of 1.2 ml) for treatment and touch-up sessions when compared with that for CosmoPlast (a mean volume of 1.9 ml).

PREVELLE SILK

Prevelle Silk is manufactured by Genzyme (Ridgefield, NJ) and distributed by Mentor (Irving, TX). It was FDA approved in March 2008. It contains 0.3% lidocaine. It is a particulate form of NASHA that is cross-linked with DVS. It has a lower concentration of HA (5.5 mg) than most products but it contains a high concentration of cross-linked HA (98%) and only 2% HA fluid gel. In a study of 45 patients, 29 patients preferred the Prevelle-treated NLF versus the side injected with Captique.[18] The vast majority (97%) of those patients preferred Prevelle Silk because it was less painful than Captique. The remainder of the studies from Prevelle Silk's package insert is based on the pivotal trials of Hylaform (Hylan B) from which it was derived.

HYLAFORM, HYLAFORM PLUS, AND CAPTIQUE

Hylaform, Hylaform Plus, and Captique are manufactured by Genzyme (Ridgefield, NJ), were first distributed by Inamed and now owned but not actively promoted by Allergan (Santa Barbara, CA). Hylaform was the first HA developed for dermal filling. It was

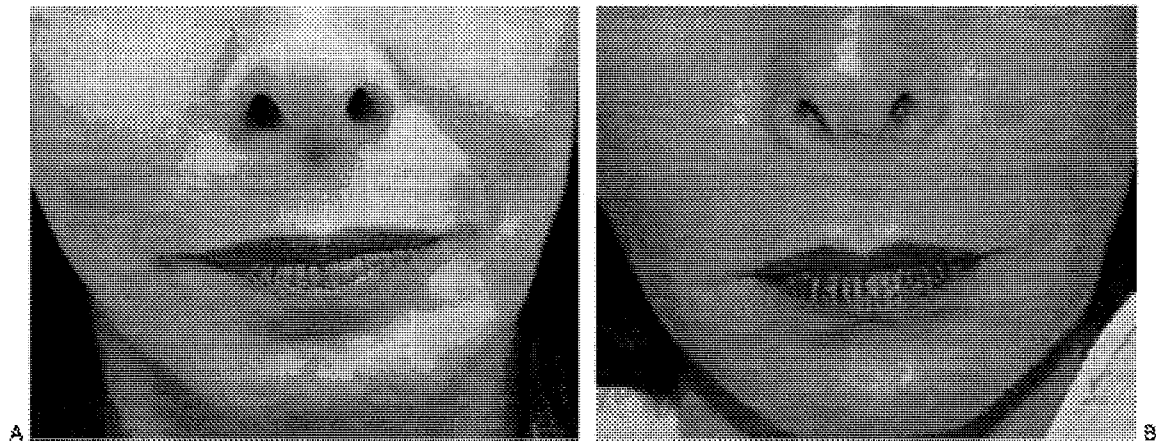

Figure 5 (A) Moderate to severe nasolabial folds before treatment with an HA filler. (B) Three months after treatment of the nasolabial folds. The patient had an initial treatment (2 syringes) and a 6-month supplemental treatment (2 syringes) of Restylane.

released in Europe in 1996 and was FDA approved in the United States in 2004. Hylaform and Hylaform Plus are avian-derived, particulate HAs that are cross-linked with DVS. Hylaform's pivotal phase III trials were conducted at eight sites in the United States with more than 300 patients.[19] It was a double-blinded, randomized trial comparing Hylaform with bovine collagen (Zyplast) in NLF augmentation. It was demonstrated that there was at least equal augmentation between Hylaform and Zyplast, lasting for up to 4 months. Hylaform Plus is a spin-off from Hylaform. It was also FDA approved in 2004. The only difference between Hylaform and Hylaform Plus is that the Plus formulation contains a larger particle size and must be injected by a 27-gauge needle. Pivotal trials compared the duration of Hylaform Plus with Hylaform in NLF augmentation and found the improvement to be equivalent at 12 weeks.[20] Captique™, also FDA approved in 2004, has the same formulation as Hylaform except that it is bacterial-based HA. It was FDA approved based on the pivotal trials of Hylaform. All three of these products are currently being phased out.

PRETREATMENT EVALUATION

Careful and thoughtful discussion about the benefits and side effects of HA soft tissue augmentation must occur with the patient before treatment. A thorough physical examination of the areas of volume loss, specific folds, and rhytides must also occur. We must also surmise and address what bothers the patient and not just what we see that needs improvement to make a plan for facial rejuvenation. We must estimate how much filler is needed and recommend a follow-up with 2 to 4 weeks to see if any additional volume is required. We have found that an early touch-up at 4 to 6 months can creates a reservoir in the skin that may make the product last longer (Fig. 5). This interim visit can also allow you the opportunity to augment another area that requires cosmetic improvement. If the fold is in an area that is influenced by muscular action, we also discuss relaxing the muscle with botulinum toxin to prolong the cosmetic improvement gained from the HA (Fig. 6). We ask the patients to refrain from any non–medically necessary blood-thinning agents for at least 7 days before injection to minimize bruising. This includes aspirin, nonsteroidal

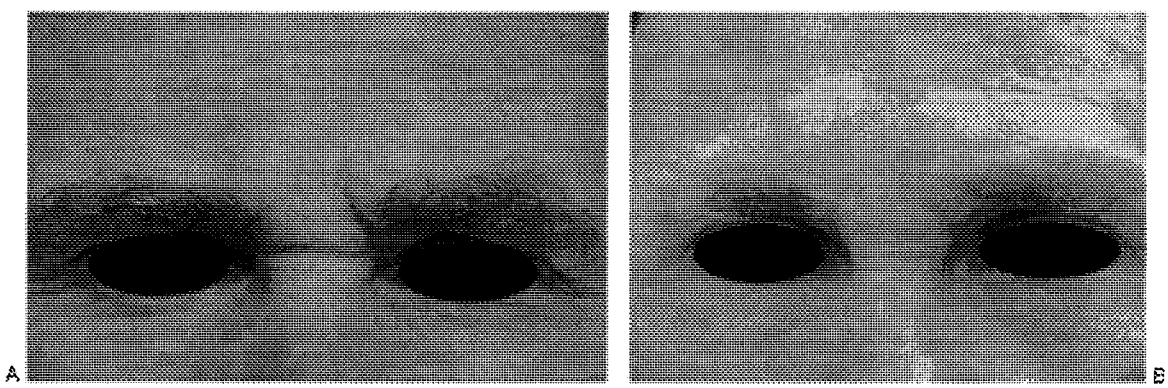

Figure 6 (A) Deep glabellar furrows before treatment with botulinum toxin and HA. (B) Two years after treatment with an HA filler. The patient had an initial treatment (0.4 mL) and one touch-up treatment (0.4 mL) 4 months later with Restylane combined with ongoing botulinum treatments.

anti-inflammatory drugs, vitamin E, and herbal preparations (ginger, garlic, gingko biloba, kava kava, St. John's wort). We document any allergies. If we plan to augment the lips, we discuss using antiviral prophylaxis against herpes virus reactivation. We have a thorough discussion of the expected side effects and what can be done to minimize them, and patient expectations must be addressed. Informed consent is either obtained at the consult or before treatment.

TREATMENT

When a patient arrives for treatment, standardized pretreatment photos are taken with a hand-held digital camera or camera system. The patient's face is thoroughly washed with cleanser and dried to remove all traces of makeup. A topical anesthetic is applied. Application of a hot, wet towel to the face can improve the absorption and enhance the effect of the topical numbing agent. After 30 to 60 minutes, the topical numbing agent is removed, and the patient's skin is again cleaned with an antiseptic like alcohol. Pretreatment with a gel ice pack also aids in patient comfort and causes blood vessel constriction, which minimizes bruising. Immediately before injecting, it is routine for us to add 0.2 mL of 1% lidocaine with epinephrine via a two-sided sterile connector into any HA that does not come premixed with lidocaine. Our personal experience is that this technique is very effective for pain control, and nerve blocks are no longer necessary for anesthesia even for lip augmentation. Control of pain is of the utmost importance. Many patients have had previously painful experiences with the HA fillers and they are reluctant to have them performed again. By decreasing the pain of the procedure, you are increasing the chance that your patient will continue the rejuvenation process with fillers in the future. Cold gel packs can be applied as needed throughout the procedure to reduce swelling and discomfort. Slow, cautious injection is also less painful, and recent studies have shown a direct correlation between the speed of injection and the number of adverse effects.[21] Minimizing the number of needle sticks also decreases the chance of bruising. Various injection techniques for HA fillers are well documented. These consist of serial puncture, linear threading, fanning, and cross-hatching. The fillers may also be injected retrograde and anterograde (push forward). We use a combination of all injection techniques depending on the type of line or fold and location on the face. The use of a 32-gauge needle when injecting products that are packaged with a 30-gauge needle can shear the particles or create smaller threads of gel so that the product can be used to augment the finest of lines. Gentle palpation or massage with cold ultrasound gel or a lubricant like Aquaphor (Beiersdorf Inc., Wilton, CT) or an antibacterial ointment can be done after treatment to ensure the product feels smooth and any small palpable deposits are flattened. Vigorous massage is discouraged because it may lead to more swelling.

SIDE EFFECTS

The most frequent types of reactions are needle marks at the site of injection, erythema, swelling, tenderness, mild pruritus, bruising, and small lumps/bumps. These are generally mild and are usually gone in less than a week. These reactions should be discussed in detail with the patient before treatment so that they are considered expected rather than true complications. Patients can also be instructed how to treat these reactions, which may hasten the resolution of the reaction. For example, we provide our patients with refreezable ice packs to take home so they can apply and reduce swelling and discomfort. If they bruise, we provide them with a sample of vitamin K cream that they can apply to speed up the resorption of the hematoma. If they feel a small lump or bump that troubles them, they can apply gentle pressure or massage to flatten the area. A follow-up appointment at 2 to 4 weeks is helpful to manage any asymmetry or to assess if more product is needed. An expected follow-up appointment at 7 days for tweaking sensitive areas like the lips and the perioribital area is also helpful. True complications are rarely seen when injecting HAs, but many of these complications directly correlate with the skill and experience of the physician-injector. These true complications include injection into or compression of vascular supply, tissue necrosis, persistent nodule formation, granuloma formation, allergic reaction, infection, and visible blue hue (Tyndall effect). It has been well documented that nitropaste and hyaluronidase must be readily available in your office for the immediate treatment of any vascular compromise.[22] Hyaluronidase and extrusion techniques are also helpful for treating persistent nodules and the Tyndall effect.

ON THE HORIZON

The production of new dermal HA fillers is increasing so rapidly that some of the below fillers may be FDA approved by the time of this article's release. The paragraphs below detail new HA products that are either currently under FDA review or will probably undergo the approval process in the near future.

Puragen is manufactured by Genzyme (Ridgefield, NJ) and distributed by Mentor (Irving, TX). It contains double cross-linked HA and a low concentration of free HA (6%) per milliliter. A small Japanese study of 10 patients compared Puragen injection with Restylane in the glabella. Two independent blinded observers found the Puragen-treated side to be superior after 12 months

in 7 patients.[23] Puragen Plus is the same formulation as Puragen except it contains 0.3% lidocaine.

Teosyal is manufactured by Teoxane SA (Geneva, Switzerland). It is a family of seven types of NASHA (Deep Lines, Ultra Deep, Global Action, Kiss, Meso, Touch-up, and First Lines). They boast the lowest protein levels and a low level of bacterial endotoxins, which is thought to reduce hypersensitivity reactions, as well as swelling and inflammation.

Revanesse is manufactured by Prollenium Medical Technologies, Inc (Ontario, Canada). This is a family of five nonparticulate NASHA products. Two of the products (ReDexis and ReDexis Ultra) contain cross-linked dissolvable dextrane beads in addition to HA, which are thought to give the products greater longevity and filling power.

Belotero is manufactured by Anteis (Geneva, Switzerland). They have two formulations of nonparticulate double cross-linked NASHA (20 mg/mL and 22.5 mg/mL) that are produced by a proprietary CPM (cohesive polydensified matrix) technology.

Atléan was recently acquired by Stiefel Laboratories, Inc (Coral Gables, FL). It is a product that contains hyaluronic gel mixed with tricalcium phosphate (Beta-TCP) particles. It is used in Europe for sculpting and volumizing the face.

Restylane Touch and Restylane Sub-Q: Restylane Touch was formerly known as Restylane Fine Lines. It is a formulation with a very small particle size and ~500,000 particles per milliliter. It is proposed for the most superficial lines. Restylane Sub-Q is a formulation with very large particle size and ~1000 particles per milliliter. It is proposed to fill subcutaneous defects and provide volume. Restylane Lipp and Restylane Vital are additional formulations available in Europe. Medicis Aesthetics is also investigating formulations of Restylane and Perlane with the addition of 0.3% lidocaine.

Juvéderm Voluma is available in Europe. It is a NASHA (20 mg/mL) that is used for facial volume restoration. There are also formulations of Juvéderm premixed with 0.3% lidocaine available in Europe.

CONCLUSION

The field of soft tissue augmentation is as rapidly changing as it is exciting. The variety of cosmetic dermal fillers available is vast. The inherent qualities of the HA dermal fillers maintain their position as the filler of choice for cosmetic skin rejuvenation. Nine HA fillers have been FDA approved as of December 31, 2008, and this number is expected to rapidly increase in the future.

ACKNOWLEDGMENTS

The authors would like to thank Karin Sorenson for her administrative, editorial, and graphics support. We would also like to thank Cristi Meyers and Kimberly Brazil for their research assistance.

REFERENCES

1. American Society for Aesthetic Plastic Surgery. Cosmetic Surgery National Data Bank: 2007 Statistics. Available at: http://www.surgery.org/public/consumer/trends/cosmetic_procedures_in_2007. Accessed December 22, 2008
2. Meyer K, Palmer JW. The polysaccharide of the vitreous humor. J Biol Chem 1934;107:629–634
3. Simoni RD, Hill RL, Vaughan M, Hascall V. The discovery of hyaluronan by Karl Meyer. J Biol Chem 2002;277:4575–4579
4. Sutherland IW. Novel and established applications of microbial polysaccharides. Trends Biotechnol 1998;16:41–46
5. Zhao XB, Fraser JE, Alexander C, Lockett C, White BJ. Synthesis and characterization of a novel double cross linked hyaluronan hydrogel. J Mater Sci Mater Med 2002;13:11–16
6. Tezel A, Fredrickson GH. The science of hyaluronic acid dermal fillers. J Cosmet Laser Ther 2008;10:35–42
7. Monheit GD, Kablik J, Yu L, Chang G, Gershovich J. Physical properties of commercial hyaluronic acid dermal fillers. Poster presented at: American Society of Dermatologic Surgery Annual Meeting; November 6–9, 2008; Orlando, FL
8. Juvéderm™ Ultra and Juvéderm™ Ultra Plus. Santa Barbara, CA: Allergan [data on file]
9. Elevess™. Woburn, MA: Anika Therapeutics [data on file]
10. Narins RS, Brandt F, Leyden J, Lorenc ZP, Rubin M, Smith S. A randomized, double-blind, multicenter comparison of the efficacy and tolerability of Restylane versus Zyplast for the correction of nasolabial folds. Dermatol Surg 2003;29:588–595
11. Wang F, Garza LA, Kang S, et al. In vivo stimulation of de novo collagen production caused by cross-linked hyaluronic acid dermal filler injections in photodamaged human skin. Arch Dermatol 2007;143:155–163
12. Narins RS, Dayan SH, Brandt FS, Baldwin EK. Persistence and improvement of nasolabial fold correction with non-animal-stabilized hyaluronic acid 100,000 gel particles/mL filler on two retreatment schedules: results up to 18 months on two retreatment schedules. Dermatol Surg 2008;34(S1):S2–S8
13. Lindqvist C, Tveten S, Bondevik BE, Fagrell D. A randomized, evaluator-blind, multicenter comparison of the efficacy and tolerability of Perlane vesus Zyplast in the correction of nasolabial folds. Plast Reconstr Surg 2005;115:282–289
14. Perlane® [package insert]. Scottsdale, AZ: Medicis Aesthetics Inc; 2007
15. Baumann LS, Shamban AT, Lupo MP, et al. Comparison of smooth gel hyaluronic acid dermal fillers with cross linked bovine collagen: a multicenter, double masked, randomized, within-subject study. Dermatol Surg 2007;33(S2):S128–S135
16. Pinsky MA, Thomas JA, Murphy DK, et al. Juvéderm injectable gel: a multicenter, double-blind randomized study of safety and effectiveness. Aesthet Surg J 2008;28:17–23
17. Elevess™ [package insert]. Woburn, MA: Anika Therapeutics Inc; 2007

18. Prevelle™ Silk [package insert]. Irving, TX: Mentor Corporation; 2007
19. Monheit GD. Hylaform: a new hyaluronic acid filler in soft tissue augmentation. Facial Plast Surg 2004;20:153–157
20. Hylaform® Plus [package insert]. Santa Barbara, CA: Inamed / Allergan; 2004
21. Glogau RG, Kane MA. Effect of injection techniques on the rate of local adverse events in patients implanted with nonanimal hyaluronic acid gel dermal fillers. Dermatol Surg 2008;34(S1):S105–S109
22. Hirsch RJ, Cohen JL, Carruthers JD. Successful management of an unusual presentation of impending necrosis following a hyaluronic acid injection embolus and proposed algorithm for management with hyaluronidase. Dermatol Surg 2007;33:357–360
23. Kono T, Kinney B, Groff W, et al. Randomized, evaluator- blind, split-face comparison study of single cross-linked versus double cross-linked hyaluronic acid in the treatment of glabellar lines. Dermatol Surg 2008; 34(S1):S25–S30